Interoffice Memorandum

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For your review & let's discuss
M. Friedman

DATE: December 29, 1994

TO: Dr. Mortimer D. Sackler
Dr. Raymond R. Sackler
Dr. Richard S. Sackler

FROM: Michael Friedman

RE: **Product Pipeline and Strategy - VERY CONFIDENTIAL**

cc J. Lang

RECEIVED
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J. J. LANG

PURPOSE

To summarize our current U.S. product pipeline and product positioning strategy.

BACKGROUND

1. Products under development or planned for development for the U.S. market are:

   1.1 OxyContin 10, 20, 40, 80 & 160 mg
   1.2 Buprenorphine patch
   1.3 Bupivacaine injectable controlled release

2. We are contemplating development of:

   2.1 Tramadol OD
   2.2 Hydromorphone OD
   2.3 Oxycodone OD
   2.4 Morphine OD

3. **Product Launch Schedule** - Based on our current development schedules we will be launching new products as follows:

3.1	1995/early 1996	Oxycodone 10,20 & 40 mg
3.2	1996/1997	OxyContin 80 and possibly 160 mg
3.3	1998/1999	Bupivacaine injectable controlled release & buprenorphine patch
3.4	2000/2001	Hydromorphone OD or Tramadol OD or oxycodone OD or morphine OD

4. **Impact of "Class" designation** - In the United States, the Opioid Analgesic market is often segmented by class. The designation of a drug in a specific class links that drug with specific prescribing restrictions and perhaps a stigma in the doctor's mind. For the purposes of this discussion, the following are the significant features of each class:

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4.1. Class II - Products in this class include single-agent opioids such as MS Contin, Dilaudid (hydromorphone), and Duragesic (fentanyl patch). This class also includes Oxycodone combination products such as Percocet, Percodan, Tylox and oxycodone combination generics. Prescriptions in this class cannot be filled by telephone order, cannot be refilled and, in some states, are subject to triplicate prescription form requirements. Class II restrictions are the most severe of those placed upon marketed drugs. Oxycodone combinations were put into Class II as a result of their abuse and the desire by regulatory authorities to better regulate their use. The indications for oxycodone combinations closely pattern the indications for which Class III drugs are used and do not parallel the indications for which single agent opioids are used.

4.2. Class III & IV- While there are specific record keeping requirements imposed upon pharmacies regarding the handling of Class III & IV drugs, both telephone prescriptions and refills of these drugs are allowed. Included in these classes are Hydrocodone combinations, codeine combinations, dihydrocodeine combinations, propoxyphene, and pentazocine.

5. The following are some significant statistics regarding Class II products:

5.1. There are approximately 1.5 Million prescriptions written for MS Contin, Dilaudid and Duragesic, per year. There are approximately 11.2 Million prescriptions written for oxycodone combinations per year.

5.2. Approximately 80% of combined MS Contin, Dilaudid and Duragesic prescriptions are written for Oncology patients (1.2 million prescriptions). A much smaller percentage, of the oxycodone combination prescriptions are written for cancer patients (8%), although the absolute number is of a similar magnitude (900,000 prescriptions).

5.3. The remainder of the prescriptions for oxycodone combination products are for the treatment of post-operative pain (47%), musculoskeletal pain (16%), and trauma (12%).

6. The following are some significant statistics regarding Class III products:

6.1. There are approximately 70 Million prescriptions written each year for Class III narcotics. This total includes: Hydrocodone combinations (34 Million), Codeine combinations (34 Million), and Dihydrocodeine combinations (approximately 348,000).

6.2. Of the large number of prescriptions for Class III prescription drugs, only 2.8% are written for cancer patients, however, this represents 1.9 million prescriptions. Note: it is important to note that the size and value of prescriptions differs from class to class and from product to product.

6.3 The balance of the 68.7 million prescriptions for Class III products are divided up between post-op (28%), musculoskeletal (21.4%), injury trauma (22%), and CNS pain (9%).

6.4. Note: We will not get into the details of the Class IV market, however, the number of prescriptions is 30 million and the dollars are $202 million.

7. **Analgesics for cancer pain** - If we were simply to look at the potential market defined by the number of prescriptions for cancer patients, we have 1.2 Million prescriptions in the Class II single agent group, 900,000 in the Class II oxycodone combination group, and 1.9 Million in the Class III group, totalling approximately 4 Million prescriptions per year. This number can be compared to our current MS Contin prescription level (included in these numbers) of approximately 750,000 prescriptions per year. While it is unlikely that MS Contin would be considered for all these Oncology prescriptions, it is still worthwhile to note that out of 4 million narcotic prescriptions written for Oncology patients, 750,000 are for MS Contin. Even more significant are the implications that these numbers have on the potential of OxyContin in this patient group.

8. **Totals Class II and Class III** - Looking at all indications, we find that the Class II single agent (MS Contin, Dilauded, Duragesic) market is 1.5 Million prescriptions or approximately $165 Million (or $110 per scrip), the Class II oxycodone combination market is 11.2 Million prescriptions or $110 Million (or $9.80 per scrip), and the Class III combination market is 68.7 Million prescriptions or $354 Million (or $5.15 per scrip), for a total between Class II and Class III of over $600 Million of potential and in excess of 80 Million prescriptions.

9. **MS Contin prescription breakdown by speciality** - Our current MS Contin business has created a "franchise" with certain physicians who routinely write prescriptions for the drug. The breakdown of specialists is as follows: Oncology/Hematology 36%, Internal medicine 22%, FP/GP 14%, Osteopaths 5%, and all surgeons 5%. This is very similar to the breakdown for Duragesic, except that Duragesic has somewhat higher numbers for internal medicine (24%) and FP/GP (18%). Surprisingly, we generate as many prescriptions for MS Contin through FPs/GPs & IMs as we do through Oncologists, however, we need to see many more doctors to generate that same number of prescriptions.

10. **Oxycodone prescriptions by speciality** - On the other hand, oxycodone combination products are prescribed along a very different specialty pattern: Primary care 30%, surgeons 21%, dentists 17%, OBGs 6% and oncology/hematology 3%.

DISCUSSION

1. **OxyContin-**

1.1. We are uncertain about when, and if, we will face generic competition for MS Contin, however, it is possible that we could see an AB rated generic in late 1995 or 1996.

1.2 We have an existing franchise with those doctors that write MS Contin prescriptions and since many of these physicians are FPs/GPs and IMs we know that they also use Class II and Class III combinations for a variety of other diagnosis/indications. The FPs/GPs and IMs may be the bridge that we can use to expand the use of OxyContin beyond Cancer patients to chronic non-malignant pain.

1.3 We believe that the FDA will restrict our initial launch of OxyContin to the Cancer pain market. However, we also believe that physicians will perceive OxyContin as Controlled-release Percocet (without Acetaminophen) and expand its use. We do not want to position OxyContin in a way that will discourage physicians from using OxyContin for chronic non-malignant pain, especially when we have studies available that demonstrate efficacy and safety for this indication.

1.4 If physicians perceive OxyContin as controlled-release Percocet it is likely that they will start to use it in place of oxycodone combinations. As physicians become more comfortable with use in the oxycodone combination market it is possible that they will also start to use OxyContin in place of Class III hydrocodone or codeine combination drugs. Therefore, it is imperative that we establish a literature to support such use.

1.5. It is not unreasonable to assume that the first target for OxyContin will be the 1.5 Million prescriptions currently generated for single-agent opioids, followed by the 900,000 prescriptions currently written for cancer patients using oxycodone combinations. This approach will lead to greater use by physicians for the patients receiving the other 10+ Million prescriptions for oxycodone combinations, for other indications. If price dies not become a significant barrier, market expansion into chronic non-malignant pain could lead to the use of OxyContin in the 68.7 million prescription Class III market. The port of entry to the oncology market will be oncologists and those FPs/GPs/IMs that currently treat cancer patients. By targeting both of these groups we will establish credibility in the Oncology market. The use of OxyContin in Cancer pain patients, initiated by their Oncologists and then referred back to FPs/GPs/IMs, will result in a comfort level that will enable expansion of use in chronic non-malignant pain patients also seen by the family practice specialists. As we build clinical literature and the FDA becomes more comfortable with our promotion we will be in a position to move our promotion more aggressively into the indications currently reserved for oxycodone combinations and Class III combinations, specifically post-operative pain,

musculoskeletal pain, injury/trauma, and CNS pain.

1.6. In summary, OxyContin will have the broadest range of use (from mild through severe pain) of any single-agent opioid and we must position it at launch in consideration of how this drug will be promoted and used in a variety of other markets. In this respect, our pricing decision will pose unique challenges.

2. **Buprenorphine Patch -**

2.1. We are very close to concluding an agreement with LTS for the buprenorphine patch.

2.2. In view of the ceiling effect associated with high doses of buprenorphine it is likely that this product will be limited to use for mild to moderate pain. Buprenorphine is currently Schedule 5 and it is likely that the buprenorphine patch will retain the same scheduling.

2.3. With virtually no narcotic prescribing restrictions, the buprenorphine patch can be in a very interesting position relative to the Johnson & Johnson Tramadol product which we expect to see launched in 1995. Between 1995 and the launch of the Buprenorphine Patch we will probably see Tramadol and Toradol continue to move a chunk of the musculoskeletal indications and some other business out of the Class III & IV categories. This will be an important shift in our markets, as the Class II, Class III & Class IV structure may start to mean less in terms of types of pain and the manner in which the physicians view narcotics based upon classification. The buprenorphine patch will provide us with an opportunity to market a drug with few prescribing restrictions, that has a novel delivery system, and which will be prescribed by doctors for mild to moderate pain.

2.4. As we develop a position with the FPs/GPs & IMs for OxyContin, it is likely that, with proper clinical support, we will start to direct the market to greater use of OxyContin for musculoskeletal and post-operative pain. When this movement starts to take place, we will start to shift our promotion to add orthopedic surgeons and other post-operative indication prescribers. This move will place us well to capitalize on the potential for the buprenorphine patch, which will probably be prescribed for musculoskeletal, CNS and post-operative pain.

3. **Bupivacaine Injectable** -The indications for the Bupivacaine injectable controlled-release product will not overlap with the indications for OxyContin or the buprenorphine patch. However, the positions that we build on formulary committees, with surgeons, orthopedists and other physicians treating musculoskeletal conditions and injuries will provide us with relationships that can be used to develop the bupivacaine injectable controlled-release. The link between our prior activities and bupivacaine injectable controlled-release will be the physician groups towards which we will be shifting our Field Force as OxyContin and hopefully the buprenorphine patch are developed.

4. As we consider the development of hydromorphone OD, OxyContin OD and morphine-

OD it is important to remember the following:

4.1 **Morphine OD** - It is likely that Kapanol or another (such as Gacell) controlled-release morphine will beat us to the US market as a once-a-day drug. Given the practices of the current managed care market, in the United States, it is going to be very difficult to pay back the investment required to launch a second controlled-release morphine OD. Further, it will be difficult for even the first morphine OD the maintain a premium price on managed care formularies against a generic BID morphine sulfate (competitor to MS Contin).

4.2. **Hydromorphone OD** - On the other hand, it is likely that our development of a hydromorphone OD could be first to market and that we could build an interesting marketing story around the product. Specifically, we could ensure that our clinical program covers the issues of metabolites and we could try to document the "side effect" story that we keep hearing from some of the pain experts. The fact that hydromorphone is a different substance will make it easier for us to obtain formulary approval at managed care organizations that will already have generic BID controlled-release morphine sulfate on formulary.

4.3. **Oxycodone OD** - Since we have a strong patent position with oxycodone BID we can spend some time developing hydromorphone and some other drugs before we start with oxycodone OD. However, oxycodone OD should be developed as a product to be launched later in the life of the OxyContin product. As our patent coverage on OxyContin expires we will want to have a once-a-day drug with which to substitute usage of OxyContin and extend the OxyContin product life.

4.4. **Tramadol OD** - With J&J spending a lot of money to develop the Tramadol franchise, the development of a Tramadol OD could provide us with a superior product to sell into their base. We do not know the status of the J&J Tramadol OD drug development, however, at the worst, as we push our product forward it becomes a valuable bargaining chip.

SUMMARY AND PROPOSED ACTIONS

If we consider the analgesic ladder as a continuum along which we position each of the products that we propose for development, the following is how we would position our proposed development program:

1. **MS Contin** currently covers most of Step 3 and reaches into Step 2. Eighty percent of the use of MS Contin is in cancer, however, over one-third of the prescriptions are written by FPs/GPs &IMs. We will continue aggressive promotion of MS Contin.

2. **OxyContin** will cover most of Step 3, all of Step 2 and could reach down into Step 1. We expect our initial promotion of OxyContin to be directed at current prescribers of single-agent opioids and oxycodone combinations; however we will not limit our promotion of OxyContin to cancer pain. We expect that over time the FPs/GPs & IMs that prescribe the drug for cancer pain will use the drug for other types of pain. We will

direct this movement through the use of clinical studies, some of which will be available shortly after launch. We hope that the use of OxyContin will expand beyond the FP/GP & IM group into the other physician groups that use oxycodone combination and Class III drugs for post-operative, musculoskeletal, injury trauma, CNS, and other pain. OxyContin will be promoted at launch with most of our sales and marketing resources.

3. **The Buprenorphine Patch**, which we hope to launch in 1998 or 1999, will cover most of Step 2 and most Step 1. We hope to sell this drug to physicians that we have become acquainted with through our promotion of OxyContin for chronic non-malignant pain and to direct the use of this drug for chronic non-malignant pain and post-operative pain. This drug should be developed as quickly as possible.

4. **The bupivacaine injectable controlled-release** will be sold to physicians treating patients for musculoskeletal disease, injury trauma and post-operative pain. Many of these physicians will have become known to us through our marketing of OxyContin and the buprenorphine patch. This drug should be brought to market as quickly as possible.

5. We propose that development of **hydromorphone OD** takes priority over development of morphine OD and oxycodone OD. The hydromorphone OD will be sold into the "step 3" market currently occupied by MS Contin, Duragesic and Dilaudid and will help to fragment what should be a very large OxyContin market position in the year 2000 - 2001 when hydromorphone OD becomes available.

6. The **OxyContin OD** product should be developed for launch sometime after the availability of hydromorphone OD.

7. We propose a development of **Tramadol OD** for launch into the Step 1 and Step 2 segment of the market. This product will allow us to supplement our promotion of the buprenorphine patch with an oral drug for mild to moderate pain which will have advantages over the then marketed BID or TID Tramadol sold by J&J.

8. The pipeline presented above provides us with a baseline that, with a bit of luck, should provide for expansion and growth of the business to the year 2000. We continue to run exposed to the threat of generics, and the possibility that technological innovation might make some of these products redundant or irrelevant. At this time, we do not know of any technology that would replace opioids within the time span covered in this paper. Another significant threat to the commercial viability of our pipeline is the availability of low-cost immediate-release narcotics. Again, we believe that the advantages of controlled-release agents can be demonstrated through proper pharmaco-economic trials and we would propose studies to support the economic viability and efficiency of our products be included in all development programs.

8. Notwithstanding the baseline presented above, the company requires additional volume and technology. We need volume to broaden our financial base and technology to improve our future viability. Commercial Development will develop a separate proposal in regards to this element of our requirements.

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